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# Pharmacokinetics and toxicity of mitomycin C in rodents, given alone, in combination, or after induction of microsomal drug matabolism

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**Summary.** The pharmacokinetics of mitomycin (MMC) was studied in Wistar rats. Up to five half-lives, the plasma concentration-time curve was biphasic. The AUC changed linearly with increasing doses between 0.5 and 7.5 mg/kg, which corresponds to 0.2 and 3 times the $LD_{50}$ value in rats. Most of the drug was metabolized, and only 1%–2% and 10%–15% of the dose was eliminated unchanged by biliary and urinary excretion, respectively. The AUC of MMC at the $LD_{50}$ is slightly less than that reported for the human MTD. Inoculation of MMC together with 5-fluorouracil and doxorubicin did not change the terminal half-life of MMC but decreased the total body clearance and the volume of distribution. The lack of significant influence of phenobarbital and 3-methylcholanthrene pretreatment on the terminal elimination half-life suggests that microsomal drug-metabolizing enzymes inducible by these compounds do not play a decisive role in the in vivo biotransformation of MMC.

## Introduction

Mitomycin C (MMC) is clinically the most widely used representative of the bioreductive alkylating agents [3, 6]. At the time of its introduction into the clinic, only bacteriological assays were available to measure its concentration in the blood and tissues [8, 19]. However, these were not sensitive enough to carry out studies on individual, small laboratory animals. Using the more sensitive high-pressure liquid chromatographic (HPLC) methods, the pharmacokinetics of MMC have been described in humans [5, 18, 23], rabbits [2], dogs [18], and recently in rats [1]. Since many biochemical, pharmacological, and toxicological studies are carried out on rats, we did a detailed study of the pharmacokinetic behavior of MMC in this species. An additional aim of the present study was to measure the elimination of the drug following pretreatment with enzyme inducers as well as during combined inoculation of MMC, doxorubicin (DX), and 5-fluorouracil (5-FU). Finally, an abbreviated toxicity experiment was carried out to investigate whether enzyme inducers might increase the lethality of MMC in mice.

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## Materials and methods

Adult male Wistar rats were used throughout the pharmacokinetic study. Their average weight was $273.5 \pm 8.4$ g. The rats were maintained on a normal laboratory diet and were not fasted before the experiment. Under urethan anesthesia (1.25 mg/kg), polyethylene cannula were inserted into the common carotid artery and the external jugular vein. The former cannula was used for blood collection, and the drugs were introduced through the latter by slow bolus injection (30–45 s). Body temperature was maintained between 36°–38° C using a heated plate regulated by a thermocouple inserted into the rectum.

MMC was dissolved in physiological saline and adjusted to pH 6.8 with 0.01 *M* sodium phosphate to give a final concentration of 1 mg/ml. A more concentrated solution of 2 mg/ml was injected only at doses above 2.5 mg/kg. The linearity of pharmacokinetics was studied with MMC doses of 0.5, 1.5, 2.5, 3.75, 5.0, and 7.5 mg/kg. Urinary, billiary, and fecal excretion has been studied at the $LD_{50}$ dose in Wistar rats, 2.5 mg/kg [17], which has been confirmed to be the $LD_{50}$ dose in this animal species in a preceding pilot study (Verweij et al., unpublished data). The FAM protocol applied in this study corresponded to the schedule used in man [11]: 600 mg/m$^2$ 5-FU, 30 mg/m$^2$ DX, and 10 mg/m$^2$ MMC injected consecutively. The rat doses were 100 mg/kg 5-FU, 5 mg/kg DX, and 1.7 mg/kg MMC. MMC was always given as the last drug. The total fluid load was 2–2.5 ml.

Blood samples (0.2 ml) were taken before and 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 min after drug inoculation. The blood was not replaced with blood or saline. Some rats died before the end of the experiment. Only those animals were considered evaluable in which samples were available from at least 2–60 min after inoculation. Bile was sampled in four rats through a cannula inserted into the common bile duct at 60-min intervals up to 4 h. Bile samples were digested for 1 h at 37° C with β-glucuronidase. For urine and feces collection, four rats injected through the tail vein were placed individually into stainless steel metabolism cages. Samples were collected at 0, 8, 24, and 48 h.

The blood samples were immediately mixed with 0.8 ml saline and kept on ice. After centrifuging, plasma was stored at −25° C. MMC is stable for at least 3 weeks under such storage conditions [7]. The HPLC method developed by den Hartigh et al. [4] was used to measure the

concentration of MMC in the plasma, urine, bile, and feces. The extraction of MMC was done with a 50% mixture of chloroform-2-propanol. The chromatographic system consisted of a C18-μ Bondapack RP column. Methanol-phosphate buffer (3:7, w/v, pH 6) was used as the eluent. Detection was carried out at 365 nm, porfiromycin served as the internal standard, and the detection limit was 1 ng/ml.

Microsomal drug-metabolizing enzymes were induced by daily i.p. injections of 100 mg/kg phenobarbital (PHB) for 4 days and by a single i.p. inoculation of 40 mg/kg 3-methylcholanthrene (3-MC) dissolved in peanut oil. The pharmacokinetic and biochemical measurements were carried out 24 h after the last injection of the inducers. For the biochemical control of enzyme induction, the livers were homogenized in a Sorvall omni-mixer in 0.05 *M* potassium phosphate buffer, centrifuged at 12,000 *g* for 20 min. The supernatant was further centrifuged at 100,000 *g* for 60 min. The microsomal pellet was resuspended in 0.1 *M* potassium phosphate buffer (pH 7.4) containing 0.1 m*M* EDTA and 25% (w/v) glycerol. Aminopyrine *N*-demethylase and benzo(a)pyrene hydroxylase activities and cytochrome P-450 and P-448 contents were measured by the methods of Nash [13], Nebert and Gelboin [14], and Omura and Sato [15], respectively.

*Pharmacokinetic and statistical analysis.* By visual inspection the plasma concentration-time curve was divided into two parts. The points of the terminal elimination phase were fitted by least-square linear regression analysis after logarithmic transformation of the data. The area under the curve (AUC) was calculated by the trapezoidal rule. It was extended to infinity, with the addition of the area calculated by dividing the last measured concentration with the terminal rate constant. The total body clearance (TBC) was then given by the equation TBC = dose/AUC, from which the volume of distribution in the terminal phase was computed: $V_B$ = dose/AUC × β.

The data were also analyzed by fitting the function $y(t) = Ae^{-\alpha t} + Be^{-\beta t}$. The values and the error of the parameters were estimated with weighted nonlinear regression on a PDP-11/23 computer using the BMD ×85 program. The values of the parameters were taken as significantly different from 0 if the error of estimates by the analysis of variance (F-test) was less than 40%–50%, depending on the number of points. In this case, the parameters were calculated from the formula AUC = A/α + B/β; the mean residence time,

$$\bar{t} = \frac{A/\alpha^2 + B/\beta^2}{A/\alpha + B/\beta}.$$

The following equations were used to calculate the apparent volumes of distribution at the terminal phase, $V_B$ = dose/AUC × β, and at steady state, $V_{SS}$ = TBC × $\bar{t}$.

The data were expressed as the mean ± standard error of the mean (SEM). The significance of difference between independent samples was calculated by the Mann-Whitney *U*-test [20].

*Toxicity of MMC in mice.* Two groups of 12 (C 57 black/Rij × CBA/Rij) F-male hybrid mice each, with and without PHB pretreatment (60 mg/kg i.p. for 3 consecutive days), were injected once i.p. with 4, 5.6, 7.8, and 10.9 mg/kg MMC. Three mice in each group were treated with each dose, and their survival was followed for 34 days. For these experiments PHB was selected because of its wide use for enzyme induction in clinical practice.

## Results

The plasma elimination of MMC was biphasic in all cases; no third phase became apparent until 2 h postinoculation, as shown on typical plasma concentration curves obtained following the inoculation of the $LD_{50}$ dose to nontreated animals (Fig. 1). The distribution phase lasted 10–20 min. Unfortunately, the estimated error of A and alpha, based on the measurements taken at 2, 5, and 10 min, was more than 50% in about half of all the experiments using the nonlinear regression program. On the other hand, the terminal portion of the curves could be always fitted accurately even if points were available only for 60 min following MMC inoculation. Thus, out of 17 experiments carried out with different doses of MMC on nontreated control rats (Table 1), the entire curve could be fitted with the required accuracy only in seven cases. The computer-calculated pharmacokinetic parameters of these animals are summarized in Table 2. Because of the aformentioned difficulties, the pharmacokinetics results used to compare the variously treated groups were calculated by the conventional method, which gave results very close to those estimated by the computer (Table 3). The AUC and the dose were related linearly with a correlation coefficient of 0.862 ($P < 0.001$) (Fig. 2). Only 1.20±0.32% of the dose was eliminated in the bile; more than 98% of this amount was already excreted by 1 h postinoculation. The hepatic clearance was 0.15±0.025 ml/min, which is around 1% of the TBC. In the urine, 12.87±3.52% of the dose was found. About 98% of the total MMC was voided by 8 h posttreatment. Since blood and urine levels were not measured in the same animals, the renal clearance was approximated

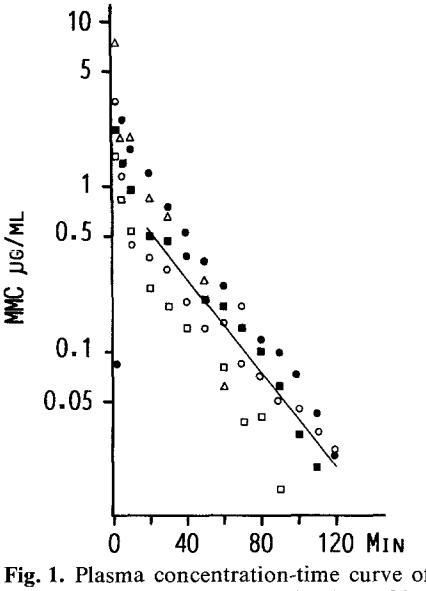


**Fig. 1.** Plasma concentration-time curve of five rats treated with 2.5 mg/kg MMC given i.v. The data of individual rats are represented by the symbols ○, ●, □, ■, and △. The terminal part of the curve between 20 and 120 min was fitted by linear regression analysis considering jointly all 43 points. The correlation coefficient was 0.887 ($P < 0.001$)

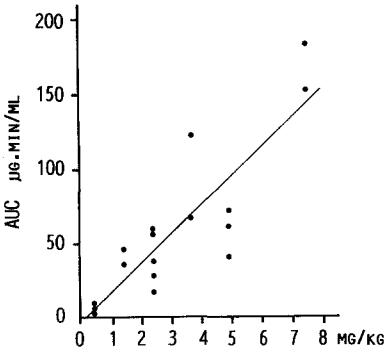


**Fig. 2.** Plot of the AUC vs dose. The equation of the linear regression line was $y = -4.21 \pm 19.84$ with a correlation coefficient of 0.862 ($P < 0.001$)

using the mean values of different rats. This gave a figure of 1.89 ml/min, which amounts to about 10% of the TBC.

Pretreatment either with PHB or 3-MC did not change the elimination half-life ($t_{1/2}\beta$) of MMC (Table 3). Regarding the TBC, a marked difference was observed between the inducers. Whereas after PHB treatment the TBC remained practically unchanged, a significant decrease occurred after 3-MC inoculation. Similar data resulted when MMC was combined with 5-FU and DX. The $t_{1/2}\beta$ did not change, whereas the TBC decreased significantly. The volume of distribution of MMC decreased parallel with the TBC; however, the differences only approached the level of significance. The biochemical measurements indicated the accepted enzyme activity changes following induction. Increased cytochrome P-450 content and aminopyrene *N*-demethylase activity were measured after PHB treatment. Following 3-MC inoculation, cytochrome P-448 appeared and benzo(a)pyrene hydroxylase activity increased

**Table 1.** Terminal half-life ($t_{1/2}\beta$), volume of distribution ($V_B$), and total body clearance (TBC) in nontreated rats

| Dose of MMC (mg/kg) | $t_{1/2}$ (min) | $V_B$ (l/kg) | TBC (ml/min) |
|---|---|---|---|
| 0.5 | 28.1 | 3.43 | 19.28 |
| 0.5 | 35.1 | 5.24 | 27.17 |
| 0.5 | 23.8 | 2.50 | 19.05 |
| 1.5 | 15.3 | 0.93 | 13.86 |
| 1.5 | 20.8 | 0.96 | 9.90 |
| 2.5 | 10.9 | 0.68 | 16.03 |
| 2.5 | 19.4 | 1.16 | 16.03 |
| 2.5 | 26.1 | 3.13 | 23.13 |
| 2.5 | 19.4 | 1.83 | 17.79 |
| 2.5 | 17.9 | 3.42 | 26.51 |
| 3.75 | 19.5 | 1.50 | 15.90 |
| 3.75 | 19.9 | 0.87 | 10.67 |
| 5.0 | 24.8 | 4.24 | 29.29 |
| 5.0 | 20.4 | 2.0 | 19.65 |
| 5.0 | 28.1 | 3.15 | 15.98 |
| 7.5 | 18.6 | 1.08 | 15.83 |
| 7.5 | 19.3 | 1.37 | 16.62 |

**Table 2.** Pharmacokinetic parameters of MMC

| Volumes of distribution (l/kg) | | | | | |
|---|---|---|---|---|---|
| $t_{1/2}\alpha$ (min) | $t_{1/2}\beta$ (min) | TBC (ml/min) | at terminal phase ($V_B$) | at steady state ($V_{SS}$) | Mean residence time (min) |
| $2.06 \pm 0.32$ | $25.69 \pm 2.5$ | $18.89 \pm 2.27$ | $2.68 \pm 0.53$ | $2.09 \pm 0.35$ | $26.93 \pm 2.48$ |

Data represent the mean ± SEM of seven rats treated with MMC alone over a dose range of 0.5–7.5 mg/kg. Only those curves were accepted for calculation in which the alpha and beta elimination phases could be described by nonlinear weighted regression analysis with an error of estimation < 50%

**Table 3.** Terminal half-life ($t_{1/2}\beta$), volume of distribution ($V_B$), and total body clearance (TBC) of MMC in variously treated rats

| Treatment + MMC dose | No. of rats | $t_{1/2}\beta$ (min) | $V_B$ (l/kg) | TBC (ml/min) |
|---|---|---|---|---|
| Control 0.5–7.5 mg/kg | 17 | $21.60 \pm 1.40$[a] | $2.21 \pm 0.33$ | $18.33 \pm 1.32$ |
| Phenobarbital pretreatment[b] 2.5 mg/kg | 4 | $19.30 \pm 1.43$ $P > 0.1$[c] | $1.76 \pm 0.26$ $P > 0.1$ | $15.36 \pm 0.56$ $P > 0.1$ |
| 3-Methylcholanthrene pretreatment 2.5 mg/kg | 6 | $20.06 \pm 0.89$ $P > 0.1$ | $1.21 \pm 0.14$ $P > 0.1$ | $8.52 \pm 0.70$ *P = 0.002* |
| FAM combination 1.7 mg/kg | 5 | $21.17 \pm 1.61$ $P > 0.1$ | $1.23 \pm 0.09$ $P = 0.1$ | $11.54 \pm 0.88$ *P = 0.02* |

[a] The values are expressed as the mean ± SEM

[b] In two additional rats the terminal half-life was the same, but their data were not included because blood sampling was started at 10 min

[c] Significance levels are given for a two-tailed test as compared to control

**Table 4.** The effect of phenobarbital and 3-methylcholanthrene treatment on cytochrome content and microsomal enzyme activities of the rat liver

| | Control | 3-Methyl-cholanthrene | Pheno-barbital |
|---|---|---|---|
| Cytochrome P-448 | – | 0.11 | – |
| | – | 0.16 | – |
| P-450 | 0.14 | – | 0.22 |
| | 0.13 | – | 0.23 |
| (nmol/mg protein) | | | |
| Aminopyrene | 3.7 | 3.8 | 7.8 |
| *N*-Demethylase | 4.6 | 4.1 | 8.5 |
| Benzo(a)pyrene | 0.13 | 0.74 | 0.14 |
| Hydroxylase | 0.23 | 1.01 | 0.18 |
| (nmol/min per milligram protein) | | | |

at least five times (Table 4). Finally, PHB pretreatment did not increase the lethality of MMC in the dose range studied. Out of 12 mice treated, 7 and 9 animals survived in the control and pretreated groups, respectively.

## Discussion

For the accurate description of the pharmacokinetic behavior of a drug, the plasma concentration must be determined at numerous time points for at least 5–6 half-lives in the same animal. Using the highly sensitive assay developed for MMC by den Hartigh et al. [4], a total of 2.8–3.0 ml blood had to be collected from the rats. Blood could be easily drawn from the carotid artery even at the late time points. The blood was not replaced, since this would have disturbed the equilibrium existing between the tissues and the central compartment during the elimination phase.

For both ethical and practical reasons the animals had to be anesthetized for the duration of the experiment. In a pilot study, pentobarbital and urethan anesthesia were compared. Although the MMC elimination curves were similar, the second anesthetic agent was selected for the following reasons: (1) pentobarbital is inactivated by the microsomal enzymes – consequently, pretreatment with inducers would have made the anesthesia unpredictable; (2) urethan as given ensured longer sleeping periods than pentobarbital at the tolerated dosage. The length of anesthesia and urethan tolerance showed great individual variations. Many animals woke up between 1.5–2.5 h after urethan injection, i.e., 60–120 min following MMC inoculation. In such cases, half of the original urethan dose had to be repeated. Unfortunately, the second drug application was poorly tolerated and about 30%–40% of the animals, randomly from all groups, expired before the planned termination of the study. The other animals had to be bled to death after the last time point. Moreover, in some randomly selected rats, infrequent blood and/or bile collection could be followed for up to 4 h without any difficulties. The slope of the terminal elimination phase was not changed by repeated urethan applications.

The curves obtained in different animals were comparable with variations in the range observed in human studies (Table 1). The plasma concentration-time curve had two phases. No evidence of a third phase was obtained until the end of the period of $5 \times t_{½}\beta$. It is important to point out that the form of the curves was similar to that drawn by Schwartz and Philips [19] from points measured up to 60 min in different nonanesthetized animals with a bacteriological assay. The $t_{½}\beta$ was approximately 25 min, i.e., approximately two times faster than in humans [2, 5, 18, 23]. The shape of the plasma concentration-time curves did not change over a dose range from 0.5 to 7.5 mg/kg, corresponding to 0.2 and 3 times the $LD_{50}$ value. The AUC changed linearly with increasing doses, whereas the half-lives and TBC did not (Table 1). Practically identical results have recently been obtained by Boike et al. [1]. These results, together with those of human studies [5, 18], definitively refute the dose-dependent nature of MMC elimination proposed originally [8].

The AUC measured in rats after the inoculation of the $LD_{50}$ was $40.5 \pm 7.9$ μg·min/ml, which is only slightly less than that obtained in humans, given the usual therapeutic dose of 10 mg/m$^2$ [5, 24]. The difference may be due to the approximately 5-fold larger volume of distribution in rats compared with the published human distribution data.

The biliary elimination of MMC accounts only for 1%–2% of the dose. Although the biliary concentration is much higher than that of the plasma, the amount excreted into the gut is too small to give a well-defined peak, even if extensive enterohepatic recirculation took place. Digestion with β-glucuronidase did not yield additional MMC, proving the absence of MMC glucuronidation. Finally, MMC was not found in the feces with the present HPLC or with the bacteriological method [19]. Also, the two methods gave identical results for renal elimination, which accounts for 10%–20% of the dose. Most of the excretion occurred during the first hours postinoculation. Renal and biliary elimination of MMC together account only for about 20% of the dose in both humans and rats; the remaining 80% is metabolized. However, no metabolites were detected by the method used.

Recently some controversy arose concerning changes in the pharmacokinetics of MMC given in combination chemotherapy. While den Hartigh et al. [5] found that TBC of MMC used in combination became larger due to the decrease of the $t_{½}\beta$, this phenomenon could not be corroborated by van Hazel et al. [23]. Using the rat model, no difference in half-life was found, but the TBC decreased significantly with a concomitant reduction of the $V_B$. 3-MC pretreatment had exactly the same effect. The reason for these observations is still to be elucidated.

The lack of any significant alteration of the $T^{1}/_{2}\beta$ following 3-MC and PHB pretreatment as well as after pentobarbital anesthesia suggests that microsomal drug-metabolizing enzymes inducible by these two compounds do not play a decisive role in the reductive activation of MMC in vivo. The plasma concentration-time curve of a compound reflects the sum of many processes occurring simultaneously in the body, such as metabolism, excretion, and drug movement between compartments. Therefore, only major changes occurring in those processes, which determine quantitatively the fate of the drug in the body, will cause pharmacokinetically demonstrable alterations. Consequently, our results do not rule out the participation of these enzymes in MMC metabolism; they only prove that changes, if present at all, were smaller than the interindividual variations between rats. This means that they would not have been revealed even in much larger groups of animals. Furthermore, the lack of increased toxicity of MMC

after phenobarbital treatment in mice proves that neither of these enzymes are involved, at least to a significant extent, in the production of activated metabolites of MMC. Our conclusion was not entirely unexpected, although there is ample evidence proving the participation of the microsomal electron transport system in the reduction of MMC to electrophilic derivatives under anaerobic conditions in vitro [8–10, 16, 19, 21]. It should be noted that several additional enzymes present in bacterial and mammalian cell lysates, e.g. flavoenzymes, can also catalyze the reductive activation of MMC [12]. It seems that the activation of MMC is a relatively nonspecific process that cannot be significantly modulated by PHB, the enzyme inducer conventionally used in clinical practice.

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